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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/869,612 | 11/13/2001 | Alesandro Massimo Gianni | GIANNI=1 | 5788 |

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| EXAMINER | |
|---|---|
| HAMUD, FOZIA M | |
| **ART UNIT** | **PAPER NUMBER** |
| 1647 | |

DATE MAILED: 06/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/869,612 | GIANNI, ALESANDRO MASSIMO | |
| | Examiner | Art Unit | |
| | Fozia M Hamud | 1647 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *17 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *2,5-13,18-26,56 and 57* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2, 5-13, 18-26, 56-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

1. Receipt of Applicant's amendment and arguments, filed on 17 March 2004, is acknowledged. Claims 1, 3-4, 14-17 and 27-55 are cancelled, and new claims 56-57 have been added. Thus claims 2, 5-13, 18-26 and 56-57 are pending and under consideration.

2. The following previous objections are withdrawn in light of Applicants amendments filed on 03/17/04:

(i) The rejection of claims 4-13, 17-26, and 55 made under 35 U.S.C. 112, second paragraph, is withdrawn.

(ii). The rejection of claims 2, 5-13, 18-26 made under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, is withdrawn.

**Specification:**

2b. The suggested format for the specification has been followed and a "Brief Description of the Figures" has been placed at the appropriate place.

**Claim rejections-35 USC § 112:**

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3a. Claims 2, 5-13, 18-26 stand rejected and new claims 56-57 are also rejected under 35 U.S.C. 112, first paragraph for reasons of record set forth in the office action mailed on 21 October 2003, pages 4-7.

Claims 2, 5-13, 18-26 and 56-57 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of preparing CD34+ cells in vivo said method comprising administering to a donor a composition comprising growth hormone and a composition comprising G-CSF, and isolating CD34+ cells from said donor, is not enabling for a method of preparing CD34+ cells in vivo, by administering to a donor a composition comprising growth hormone "derivatives or any factor inducing growth hormone release", and a composition comprising G-CSF, and isolating said population of circulating cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, practice the invention commensurate in scope with these claims.

Applicants argue that instant specification defines derivatives of growth hormone and also provides numerous representative examples as well as guidance as to modifications that can be made. Applicants point out that the art of growth hormone, and in particular human growth hormone is well studied and that there are many prior art patent publications disclosing functional derivatives of growth hormone. Applicants further argue that those skilled in the field of growth hormones were well aware of growth hormone releasing factors and functional derivatives at the time of filing. Thus, Applicants conclude that the claimed invention is fully enabled.

These arguments have been fully considered but are deemed unpersuasive. The instant specification discloses that growth hormone derivatives include naturally-occurring derivatives, variants and metabolic

products and describes growth hormone derivatives as molecules which differ structurally from growth hormone but which conserve the function of growth hormone. However, the specification fails to disclose one single derivative that enhances the "mobilization or peripheralization effect of G-CSF" to increase the number of circulating CD34+. The issue is not whether there are numerous growth hormone derivatives, but the issue is whether "all possible" growth hormone derivatives will enhance the "mobilization or peripheralization effect of G-CSF" to increase the number of circulating CD34+. Applicants are correct in that there are numerous derivatives of growth hormone, for example U.S Patent 5,597,709 cited by Applicants, discloses two such derivatives, hGHV-2(88) which binds to growth hormone receptors and produces a downstream response similar to that of wild type human growth hormone, and hGHV-3(53) which also binds to the receptors, but results in no such downstream response is produced. Therefore, hGHV-2(88) which an agonist of human growth hormone would be expected to have similar effect as growth hormone, while hGHV-3(53), an antagonist would be expected to inhibit normal growth hormone activity. Thus, these two growth hormone derivatives would have opposite effects. With respect to "factor inducing growth hormone release", Applicants have not disclosed one single such factor that is shown to enhance the "mobilization or peripheralization effect of G-CSF" to increase the number of circulating CD34+. The instant specification discloses that the administration of recombinant growth hormone with G-CSF results in doubling or tripling the mobilization of CD34* cells in the blood stream, (see Example 7). However, the specification does not disclose

that the administration of any "derivative" or "factor inducing growth hormone" with G-CSF results in increase in CD34+. Again the issue is not existence of growth hormone releasing factors, but the fact the Applicants have not shown one single growth hormone releasing factor which increases the circulating CD34+ cells when administered in conjunction with G-CSF. Therefore, the disclosure that the administration of rhGH in conjunction with G-CSF stimulates the mobilization of CD34+ cells, is clearly insufficient support under the first paragraph of 35 U.S.C. § 112 for claims which encompass "all'" possible growth hormone derivatives and factors that induce growth hormone release.

***Claim rejections-35 USC § 103:***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4a. Claims 2, 5-13, 18-26 stand rejected and new claims 56-57 are rejected under 35 U.S.C. 103(a) as being unpatentable Haas et al (1995) in view of Murphy et al (1992), as set forth in the office action mailed on 21 October 2003, pages 8-10.

Applicants only addressed the Murphy et al reference. Applicants have not addressed the Haas et al reference, which teaches that the administration of G-CSF increased the level of circulating CD34+ cells.

Applicants argue that the Murphy et al reference dos not teach or suggest that growth hormone stimulates the mobilization of hematopoietic progenator cells to the circulation. Applicants argue that increased stem/progenitor number in the marrow or spleen does not necessarily lead to progenitor cell mobilization to the periphery, which requires release of proteases and other mechanisms.

This argument is not found persuasive. Haas et al reference teaches that the administration of G-CSF increased the level of circulating CD34+ cells. Haas et al teach that following the administration of G-CSF harvests containing between $2.2 \times 10^{6}$ and $21.6 \times 10^{6}$ CD34+ cells/kg of body weight were obtained, (see page 251, bottom of column 2). Therefore, the primary reference, (Haas et al) establishes that the administration of G-SCF results in circulating CD34+ cell number above the range recited in instant claim 6. Murphy et al reference is relied upon, because it discloses that the administration of recombinant human growth hormone (rhGH) exerts significant direct hematopietic growth promoting effects in vivo and may be of potential clinical use to promote hematopoiesis in the face myelotoxic therapy, (see abstract and page 1447). Thus, the Murphy et al reference suggests that growth hormone may have potential clinical implications to promote hematpoiesis. With respect to the argument that progenitor cell mobilization requires the release pf proteases and other mechanisms, this argument is addressing limitations not recited in the instant claims.

Therefore, the combined teachings of Haas et al and Murphy et al render the claimed invention obvious, because Haas et al teach that the administration

of G-CSF increased the level of circulating CD34+ cells, and Murphy et al teaches the growth hormone exerts a significant effect on hematopoitic progenitor cell. Thus, one of ordinary skill in the art would have an expectation of success that the administration of these agents together would have synergistic effect.

***New Rejections Necessitated by Applicants' Amendment:***

***Claim rejections-35 USC § 112, second paragraph:***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 2, 5-13, 18-26 and 56-57 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

5a. Claims 2, in line 8, recites ".....to further increase in said donor the number of circulating CD34+ cells.....*beyond that achieved by G-CSF alone*.....", which renders the claim indefinite, because the metes and bounds of the claim can not be ascertained. The claim does not recite what is the number of circulating CD34+ cells obtained after G-CSF administration and how much more should the administration of the growth hormone achieve. Appropriate correction is required.

5b. Claim 7, recites ".....about 500 or more..." and claims 10 and 12 recite "...about 1 x $10^{5}$ or more, ...", "...about 8 x $10^{6}$ or more....", respectively, which render these claims indefinite, because it is unclear how much more or less than

the recited number is intended to claim. For example, does Applicants intend to claim 450, 499, 520 CFU-GM and how much more than this number? The metes and bounds of the claims are unascertainable.

5c. Claim 56 recites "....is administered at a different time than.....", however, it is unclear whether the growth hormone composition should be administered few days before or after, few minutes before of after or weeks before or after the G-CSF administration. Appropriate correction is required.

***Conclusion:***

6. No claim is allowed.

***Advisory Information:***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Fozia M Hamud whose telephone number is (571) 272-0884. The examiner can normally be reached on Monday, Thursday-Friday, 6:00 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary L Kunz can be reached on (571) 272-0887. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Fozia Hamud

Patent Examiner
Art Unit 1647
14 June 2004

GARY KUNZ
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